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A Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Rifaximin for the Prevention of Travelers' Diarrhea in US Military Personnel Deployed to Incirlik Air Base, Incirlik, Turkey

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Background. Infectious diarrhea is an important problem among travelers and deployed US military overseas causing substantial morbidity due to acute illness and may result in burdensome postinfectious sequelae.
Methods. The nonsystemic antibiotic rifaximin was evaluated for prevention of travelers' diarrhea (TD) in a US military and civilian adult beneficiary population in a randomized, double-blind, placebo-controlled clinical trial. In all, 100 volunteers deployed to Incirlik Air Base, Turkey, received rifaximin 1,100 mg once daily or placebo for 2 weeks, and participants were followed daily for 2 weeks.
Results. In an intention to treat analysis ($n = 95$), TD (based on subjects meeting case definition or early treatment) developed in 6.3% (3 of 48) of the rifaximin group compared with 19.2% (9 of 47) in the placebo group (Fisher's exact test $p = 0.07$). Rifaximin provided 67% (95% confidence interval, −13% to 91%, $p = 0.07$) protection against TD. Rifaximn 1,100 mg once daily was well tolerated with no observed differences in adverse events, whether solicited or unsolicited among the two treatment groups.
Conclusions. Rifaximin may represent an option among military personnel on deployment for prevention of TD with supportive future studies that consider deployment length, settings, and operational situations where widespread use of chemoprophylaxis may increase force health protection without undue risk during critical deployments.

Historically and in modern times, infectious diarrhea among deployed US war fighters has posed a significant health threat despite advances in field preventive measures.[1–3] Rifaximin, a nonsystemic, gut-selective antibiotic, indicated in the United States for the treatment of TD caused by noninvasive strains of *Escherichia coli*, has the potential to address a number of the current concerns associated with the burden and management of infectious diarrhea in specific deployment settings. Given the high operational tempo as well as potential complication of giving multiple doses of antibiotics along with other chemoprophylactic regimens (eg, doxycycline for malaria), a single high dose daily (QD) regimen was evaluated for TD prevention in a deployment setting.

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Methods

Subjects were military beneficiaries traveling from the United States, with most staying at Incirlik Air Base, Incirlik, Turkey, for 14 days. Subjects were eligible for inclusion in this study if all of the following criteria were met: ≥18 years of age, in good health, and if female, met criteria for non-childbearing potential, or had a negative urine pregnancy test at screening and agreed to use a medically approved method of birth control. Exclusion criteria were as follows: antibiotic use within 7 days, antidiarrheal medication within 24, hypersensitivity or allergy to rifaximin or rifampin, acute diarrhea during the 7 days prior to enrollment, or within 24 hours after ingesting initial dose of study drug. Treatments were randomly assigned to consecutive numbers by using an allocation ratio of 1 : 1 in blocks of four for either oral rifaximin 1,100 mg QD (two 550 mg tablets) or matching placebo QD for 14 days. Salix Pharmaceuticals, Inc. (Morrisville, NC, USA) provided the interventional products in sequentially

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labeled bottles. Subjects were instructed to take study drug every morning with breakfast, and missed doses were to be taken with the following meal.

TD was defined as the coexistence of acute diarrhea (≥3 unformed stools within a 24-h period) and one or more of the following signs or symptoms of enteric infection: abdominal pain or cramps, moderate to severe increase in intestinal gas, nausea, vomiting, fever (≥37.8°C), fecal urgency, tenesmus, or gross blood and/or mucus in the stool. Stools were defined as formed (retained shape), soft (assumed shape of container and could not be poured, but would not hold form if placed on a surface; often had a custard or pudding-like consistency), or watery (could be poured). Additionally, subjects who had diarrhea and took a medication specifically for relief from the symptoms of diarrhea were categorized as having TD.

Enteric symptoms were assessed via daily subject diary entries and weekly clinic visits. Adherence was assessed during weekly follow-up visits through pill counts and interview. In addition, safety was assessed by monitoring adverse events. Excluding preestablished weekly visits, subjects could go to the clinic at any time of the day throughout the study on an informal basis. Stool specimens were collected for the purpose of conducting etiological agent analyses; however, only five acute specimens were submitted, and, therefore, results of these analyses will not be reported herein.

A target enrollment of 100 subjects with 50 subjects randomly assigned to each treatment arm was based on the relative risk of developing TD based upon analysis of time to first unformed stool (TFUS), an estimated 40% attack rate from prior studies at Incirlik,[4,5] and a hazard ratio reported in a previous study of rifaximin for the prevention of TD in travelers to Mexico.[6] Participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. A protocol deviation in assignment of study participants to treatment group occurred whereby study personnel who were responsible for assigning treatment selected the intervention arbitrarily from the secured drug storage cabinet which resulted in nonsequential assignment of study drug.

The primary efficacy end point was the relative risk of TD during 14 days of treatment with rifaximin relative to placebo based upon the TFUS (defined as the number of hours from the first dose of study drug to the first of three occurrences of an unformed stool within 1 d meeting the definition of TD) associated with TD using the Cox proportional hazards model with a two-sided test at a significance level of 0.05 (Stata Version 10, StataCorp, College Station, TX, USA). Subjects who terminated for reasons other than treatment failure or who completed the entire 14-day treatment period without meeting the definition of TD were noted as having a censored TFUS as of the last available daily subject diary information.

The study protocol was approved by the NAMRU-3 Institutional Review Board in compliance with all applicable Federal regulations governing the protection of human subjects, and all subjects provided written informed consent.

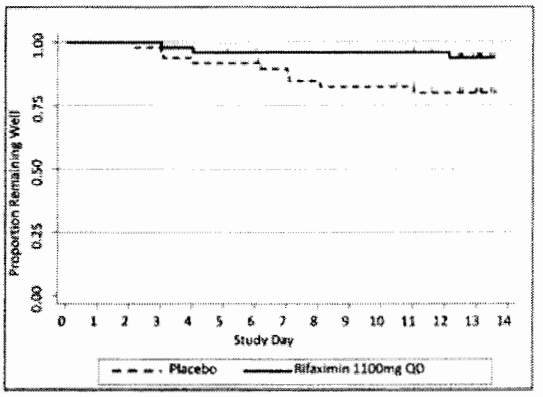

Figure 1 Probability of not experiencing diarrhea during the first 14 days in Turkey in participants taking 1,100 mg of rifaximin once daily compared with placebo (log-rank test, $p = 0.051$), intention to treat population.

Results

Between July 2007 and February 2008, 100 subjects were randomized to receive rifaximin 1,100 mg ($n = 50$) or placebo ($n = 50$) once daily for 14 days. There were no differences between treatment groups in baseline demographics. The median age was 36 years, 88% were males, and 73% were whites. One subject in the rifaximin group developed TD 4 hours after initiating treatment and was excluded from analysis. One volunteer in the rifaximin group and three volunteers in the placebo group were lost to follow-up. The remaining 95 subjects were included in the intention to treat analysis where 6.3% (3 of 48) of the rifaximin group developed TD compared with 19.2% (9 of 47) in the placebo group (Fisher's exact test $p = 0.07$; Table 1). Based on a time-to-event analysis (Figure 1), it was observed that the rifaximin group resulted in a hazard ratio of 0.29 [95% confidence interval (CI) 0.08 to 1.09; $p = 0.07$] and resulted in an estimated protective efficacy of 67% (95% CI −13% to 91%; Fisher's exact test $p = 0.07$).

Table 1 Efficacy of rifaximin in prevention of TD, intention to treat analysis

Parameter	Rifaximin ($n = 48$)	Placebo ($n = 47$)	p Value
TD, *n* (%)	3 (6.3)	9 (19.2)	0.07
Developed TD	3 (6.3)	7 (14.9)	0.2
Developed treated TD	0 (0)	2 (4.3)	0.2
Terminated early with no diagnosis of TD, *n* (%)	2 (4.2)	3 (6.4)	0.7
Developed mild diarrhea without TD, *n/n* (%)*	9/45 (20.0)	8/38 (21.1)	0.9

TD = travelers' diarrhea.
*Excludes subjects meeting TD definition.

Among 13 subjects (4 rifaximin, 9 placebo), adherence to self-dosing could not be ascertained ($n = 11$), and 2 failed to adequately complete their daily diary, and outcomes were obtained by report during weekly visit. There were no observed differences in adverse events, whether solicited or unsolicited among the two treatment groups (data not shown).

Discussion

In Turkey where diarrheagenic *Escherichia coli* are the major pathogens,[4,5] the rate of protection against TD with rifaximin observed in this study (67%) was similar to that observed in a prior study by DuPont and colleagues[6] among student travelers to Mexico. The design of this study is unique from previous rifaximin prophylaxis trials because of the higher rifaximin daily dose (1,100 mg) administered. A safe and effective QD dosing regimen of rifaximin would be more convenient and potentially more cost effective versus a twice daily (BID) or three times daily (TID) dosing regimen. Although unclear, one wonders if a higher QD rifaximin dose of 1,100 mg might also have a residual protective impact seen with more frequent daily dosing regimen at lower rifaximin doses (eg, 200 mg BID or TID). Alternatively, QD scheduling at any dose may not be as effective as BID dosing given the possibility of a therapeutic trough with QD dosing, although in the DuPont and colleagues[6] study, efficacy was observed with rifaximin 200 mg QD dosing.

This study has important limitations including inadequate power due to lower than anticipated attack rate, limited microbiological outcomes, nonsequential treatment allocation, as well as issues of adherence ascertainment and to a lesser extent daily diary completion among enrollees. Despite these deficiencies, there was no discernable effect of the nonsequential treatment allocation on primary outcomes, although such an effect cannot be ruled out. Furthermore, restricting analysis to those for whom adequate adherence and outcome ascertainment could be assessed resulted in no appreciable change in the primary outcome with an estimated protective efficacy 71% (−34% to 94%; Fisher's exact $p = 0.14$).

Given the potential harms of long-term daily antibiotics in a population at risk for trauma-associated infections (including enteric trauma) and impact on individual and community microbiomes, it is uncertain that antimicrobial chemoprophylaxis would offer a practicable solution during most extended military deployments (which historically have averaged about 3–6 mo). However, there are a number of relevant settings including port visits, in special operations forces, or in the initial phase of deployment settings where risk of TD is highest and the consequences of heat injury are frequent, where chemoprophylaxis may offer an acceptable solution. Further studies to explore the efficacy and safety of TD chemoprophylaxis in these populations and settings are warranted.

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Disclaimer

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Clinical Treatment of Nondysentery Travelers' Diarrhea During Deployment

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Learning Objective

Readers will be able to answer the following question in such a manner as to be of significant use in their official duties:

Question: When do I give antibiotics in the setting of traveler's diarrhea while deployed?

Clinical Vignette

A 26-year-old male active duty USMC First Lieutenant, on his first deployment to Iraq, presented to the medical clinic with one and a half days of loose stools. Over the previous 24 hours he reported four liquid bowel movements without gross blood. He also reported nausea without vomiting, abdominal cramping, and a headache. He denied any fever, chills, or night sweats. The patient had been in theater for approximately 4 months, and 2 days before his symptoms began he had the opportunity to sample the local cuisine. He denied known infectious contacts, use of any self-treatment, or any comorbid illnesses. On exam he was afebrile, his blood pressure and pulse were 128/82 and 84 while seated and 110/75 and 101 after standing for 3 minutes with lightheadedness. Respirations and oxygen saturation were within normal limits. Mucous membranes were slightly dry. Abdominal exam was benign except for mild diffuse tenderness. Skin turgor was normal. What is the best management for this case?

Clinical Problem

Infectious diarrhea historically has been a major problem for deployed military forces and continues to be the most common illness incurred by deployed U.S. military personnel. Although diarrheal illness is unlikely to cause death, it can result in incapacitating symptoms, causing loss of person-days, medical evacuations, and diminished job performance.[1-5] A major goal for providers treating deployed military personnel is to provide therapy that will effectively return patients to a full duty status as quickly as possible, thus minimizing the adverse effect on overall operational readiness of deployed units. Problems such as patient attitude on seeking care, failure of proper hydration early in the course of disease, and less than optimal use of empiric antibiotic treatment are obstacles to achieving this goal.

A lack of sufficient education concerning the importance of early presentation for care exists, and studies have shown deployed troops often do not seek medical attention in a timely fashion. Austere forward deployed settings increase the risk for dehydration due to ambient temperatures and rigorous working conditions, magnifying the importance of proper oral hydration treatment (ORT). Frequently however, troops do not start ORT early enough, and often use too small an amount or improper fluids to maintain hydration. Evidence exists that early initiation of empiric antibiotic treatment provides more rapid resolution of symptoms, but this practice management technique is not always exercised by the deployed military provider.

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Epidemiology

Definition

Travelers' diarrhea (TD) is one of the most common problems for persons traveling abroad. Although usually thought of as an illness for short-term travelers (<2 weeks), epidemiologic studies evaluating disease and nonbattle injury rates have also consistently identified infectious gastrointestinal illness in the top five reasons for clinic visits among individuals living in developing regions for extended periods, including populations such as deployed military personnel.[6] The formal criteria used to define TD is three or more loose stools over a 24-hour period along with another enteric symptom, such as abdominal cramping, nausea, vomiting, or fever, fecal urgency, or the passage of bloody or mucoid stools.[7–9] Most TD will resolve spontaneously over 3–5 days; however, many individuals must change their plans, experience work degradation, and require medical care, confinement to bed rest, or even hospitalization.

Incidence and Impact in the U.S. Military

The health threat associated with infectious diarrhea has been significant for U.S. military operations in all wars and conflicts from the American Revolution to the present operations in Iraq and Afghanistan.[3,10,11] A meta-analysis of 30 studies of TD epidemiology among U.S. military and similar populations, published between 1990 and 2005, found an average monthly diarrhea attack rate of 29%. More recently, self-report studies have indicated a cumulative incidence of over 75% for troops participating in Operation Iraqi Freedom (OIF) and over 50% in Operation Enduring Freedom (OEF) in Afghanistan.[1–5]

Recent studies have elucidated that these common health events can result in potentially significant degradation in operational readiness. A systematic review found a median probability of 27% for sick-in-quarters and/or short-term incapacitation and a requirement for intravenous hydration in up to 18% of deployed military personnel with diarrhea.[6] In recent OIF/OEF surveys, nearly half of the troops who developed diarrhea stated it was severe enough for them to seek medical care with 45% reporting decreased job performance for a median of 3 days.[3] Further adverse outcomes on operational readiness include intravenous rehydration requirement (30%), confinement to quarters (17%; median of 2 days), missing a patrol due to their illness (8.7%), and fecal incontinence or inability to access a toilet during an illness episode (31.9%).[2]

Survey studies show that only about one-quarter of troops present to a treatment facility, and of those who do, it is often after 24–36 hours of symptoms. If it is emphasized that troops present for care at the onset of uncomfortable diarrhea, prompt treatment initiation can limit the duration of illness to less than 1 day in most cases. This would be a great benefit in reducing the amount of time individuals experience diminished work performance, reducing the risk of a dehydration illness, thus greatly increasing the efficiency of individuals and the unit overall.

Etiology

Loose or liquid bowel movements are not always because of an infectious etiology. For troops who have recently arrived in an operational theater there are various causes to consider including changes in diet, disruption of normal meal patterns because of time-zone change, new use of a medication such as antimalarial prophylaxis, adjustment to a new environment, or the stress associated with deployment. These reasons, however, usually do not result in a persistent pattern of loose stools accompanied by enteric symptoms, such as abdominal cramping, nausea, vomiting, or fever.

Well-performed etiologic studies of travelers' diarrhea identify one or more potential pathogens in only 50–60% of stools from acute cases, with bacterial etiologies most frequently found.[6,12] A majority of the unidentified etiologies are suspected to be due to bacteria based on high levels of antibiotic treatment efficacy (exceeding 90%) in placebo controlled treatment trials[13–17] and recent studies utilizing enhanced detection methods (i.e., polymerase chain reaction [PCR]-based methods) identifying bacterial etiologies from among formerly "unknown" classification.

Among military travelers deploying overseas, numerous infectious organisms cause TD and the etiologic agents are very similar throughout the world with enterotoxigenic *Escherichia coli* (ETEC) being most common.[6] Pathogen prevalence, however, has been shown to have regional differences, with *Campylobacter* and other invasive pathogens being most common in Southeast Asia, accounting for nearly one-quarter of all cases.[18,19] *Shigella* has been noted to be a relatively frequent pathogen in sub-Saharan Africa and enteroaggregative *E. coli* (EAEC) is an emerging pathogen accounting for a relatively large percentage globally among both military and civilian travelers.[6,20–22] Following bacterial diarrhea, viruses are the next most common, generally responsible for about 5–10% of infectious diarrhea among travelers.[23] Among military travelers, norovirus and rotavirus were reported as responsible for 8% and 4%, respectively, in a systematic review.[6] Norovirus has been a reported major cause of gastroenteritis outbreaks on Navy ships[24,25] and during initial stages of combat operations.[26–28] Finally, parasites including *Cyroptosporidium hominis*, *Cyclospora cayetanesis*, *Entamoeba histolytica*, *and Giarida lamblia*, which are the most common, occur with some frequency (<5%) but generally present as a pattern of insidious onset of persistent diarrhea rather than an acute illness.[9,29–31]

Prevention

Preventive medicine activities, such as surveillance, good hygiene practice, methods to ensure use of safe food and water, and outbreak management are vital strategies for prevention of TD among deployed military troops. Education of deployed military personnel, their medical providers, and military commanders ultimately responsible, is paramount to ensure the best mitigation policies and practices are utilized. The scope of this article, however, is on treatment of TD, and public health aspects of prevention will not be addressed.

Treatment Options

Many treatment regimens for TD have been studied over the years such as oral rehydration, empirical antimicrobial therapy, nonantimicrobial treatment with antisecretory or antimotility agents, and a variety of combinations. The goal for all treatment considerations is to prevent unnecessary morbidity, therefore, ensuring hydration is a fundamental aspect in any management strategy. Furthermore, for military populations, a very important aspect of treatment is to use an option that resolves the illness as quickly as possible, enabling the service member to resume duties in a timely fashion thus minimizing the effect on the unit's mission capabilities.

Oral Rehydration

Adequate fluid and electrolyte balance is a cornerstone of any treatment regimen. Added concern for dehydration in affected military personnel relates to up-tempo operations, harsh environmental conditions (high heat and humidity), and intense physical activity, further increasing risk of dehydration during a diarrheal illness. The coupled transport of sodium (plus water and other electrolytes) through active absorption of glucose or amino acids is the physiologic basis for the efficacy of ORT.[32,33] This is best accomplished with the use of fluids similar in osmolarity and electrolyte content to the World Health Organization (WHO) oral rehydration solution (ORS) formula. Lower osmolarity solutions, such as the 2002 WHO OSR, improve intestinal absorption of fluids compared to formulas high in osmolarity. Other fluids with high glucose content and high osmolarity, although better than nothing, are not as advantageous as a lower osmolarity fluid choice. Drinks highly sweetened can increase intestinal fluid loss because of osmotic diarrhea. Apple juice, nondiet soft drinks, and Jell-O are extremely high in sugars with 6% or more glucose concentration.[23] Sports drinks such as Powerade (The Coca-Cola Company, Atlanta, GA) and Gatorade (The Gatorade Company, Chicago, IL) have improved electrolyte balance over water alone, but have a higher carbohydrate content compared to the WHO formula and also have a lower electrolyte replacement capability. Other commercially produced fluids similar to the WHO formula are listed in Table I. Various energy drinks such as Red Bull (Red Bull, Inc., Santa Monica, CA) or Rockstar (Rockstar, Inc., Las Vegas, NV), among others, are poor choices as an ORS. These products are very high in carbohydrate content, have lower sodium replenishment capability than proper ORS, and have a high osmolarity, possibly exacerbating diarrhea and reducing intestinal absorption of fluids.[34] They also contain large amounts of caffeine which can cause a diuretic effect, further worsening a volume-depleted condition.[35] Table I briefly summarizes the electrolyte content and osmolarity of some available fluid choices for hydration of troops with diarrheal illness.

When preparing for deployment, military medical providers should attempt to ensure fluids with adequate ORS capability are included in their list of supplies. Obtaining a variety of flavors may help achieve compliance among troops who may have different taste preferences.

If commercially prepared ORS formulas are not available, which is often the case in military deployments, a basic emergency solution can be made. A quick formula recommended by CDC is to add one teaspoon of salt and 2–3 tablespoons of sugar or honey to a liter of water.[23] This lacks bicarbonate provided by the WHO ORS but is easy to prepare and will help maintain blood volume and tissue hydration. To help improve compliance of solution use, commercial flavor packets, such as those used to flavor water, could be added to the medical supply checklist. Another field expedient formula is to mix a cup of orange juice or other fruit juice with 3 cups of water and 1 teaspoon of salt.

Nonantibiotic Therapy

Antisecretory agents such as bismuth subsalicylate (BSS) have long been used for the symptomatic treatment of TD. BSS reduces the number of stools passed in TD and is helpful in reducing nausea, but does not limit the duration of the disease.[36,37]

TABLE I. Comparison of Osmolarity and Electrolyte Content of Fluid Choices for Oral Rehydration Therapy

	CHO g/L	Na mmol/L	CHO:Na	K mmol/L	OSM mOsm/kg
Rehydration Formulas[a]					
WHO ORS	13.5	75	1.2	20	245
CeraLyte 70 (Rice-Base Carbohydrate)	40	70	3.1	20	235
Pedialyte	25	45	3.1	20	250
Sports Drinks[b]					
Gatorade	45	20	13	3	330
Powerade	60–80	~10	~6	~3	346–391
Powerade Isotonic	76	12	~6	~4	295
Other Fluids[c]					
Red Bull Energy Drink	108	35	~3	0	601
Apple Juice	690	3	230	32	694–773
Chicken Broth	0	250	—	8	500

Sources: [33,37,54], www.thecocacolacompany.com, www.powerade.com, nutrition labels viewed on www.dietfacts.com.

[a]Consider as first line choice for oral rehydration based on low osmolarity and proper electrolyte replacement distribution and a base of 30 mmol/L. [b]Consider as alternative if first line choices above (or homemade mixtures as described in article text) are unavailable. [c]Not recommended as rehydration for patients with infectious diarrhea.

Antimotility agents have been used for the treatment of diarrhea for approximately 50 years. Diphenoxylate hydrochloride with atropine (Lomotil, Pfizer U.S. Pharmaceuticals, New York, NY) was the first developed, and was licensed in the U.S. in 1960. Loperamide is the agent now more widely used because of better efficacy in trials and its favorable side effect profile.[9] The principal mechanism of both is increased fluid and salt absorption because of slowed movement of the gut luminal column.[37]

Antibiotics

As stated earlier, bacterial enteropathogens are the most common cause of travelers' diarrhea. Therefore, antibacterial drugs should be considered effective for treatment of TD assuming susceptibility. Several choices are effective for short-term travelers. Commonly used regimens such as doxycycline and trimethoprim-sulfamethoxazole (TMP-SMX) are now not as useful because of drug resistance,but fluoroquinolones have shown great efficacy and remain the most predictably active empiric therapy throughout most parts of the world. However, regions with *Campylobacter* predominance, most notably in Southeast Asia, have had an emergence of high levels of fluoroquinolone resistance.[19,38–40] In Thailand, numerous surveys among deployed U.S. military personnel have shown *Campylobacter* species to account for as many as 60% of diarrheal cases.[38] Tribble et al. demonstrated lack of efficacy for levofloxacin as empiric therapy in a setting of high rates of fluoroquinolone resistant *Campylobacter jejuni*.[19] In cases where *Campylobacter* infections are considered likely, azithromycin has been shown to be effective and should be used.

Over the years, a variety of regimens have been investigated in many different studies including single-dose regimens and use along with an antimotility agent. In 2000, a Cochrane Collaboration meta-analysis of nine trials demonstrated a statistically significant reduced time to last unformed stool in those receiving antibiotics, from an average of 50–93 to 16–30 hours.[8] A secondary endpoint assessing for cure indicated treatment with antibiotics resulted in a greater number of participants being cured by 72 hours.

It should be noted for individuals with diarrhea secondary to viruses, antibiotics will not be effective, although symptoms will usually resolve in 24–72 hours. Those whose symptoms are caused by parasites may not improve with recommended empirical antimicrobial therapy.[41]

Antibiotics Plus Antimotility Agents

Adjunctive use of an antimotility agent (loperamide) along with an antibiotic has been demonstrated to be safe and efficacious, exhibiting improvement over the use of antibiotics alone. Most recently, a study performed among a deployed military population in Turkey compared single-dose levofloxacin to single-dose azithromycin, along with loperamide added to both regimens.[42] The medications showed good results with respect to time to last unformed stool (TLUS) with a median of 3 hours for levofloxacin and 13 hours for azithromycin. Both antibiotics demonstrated immediate resolution of symptoms (no additional unformed stools) in 25% of participants after antibiotic receipt. One meta-analysis of several studies showed a comparative advantage to adding loperamide to an antibiotic treatment regimen.[43] Most studies independently demonstrated combination regimens offer an advantage over antibiotic treatment alone with higher odds of clinical cure in the first 24 and 48 hours after treatment initiation. One study in the review which failed to demonstrate any trend toward advantage with loperamide adjunctive treatment was one in which a single-dose fluoroquinolone regimen was used in a *Campylobacter*-predominant setting (this study predated the emergence of fluoroquinolone resistance).[44]

Areas of Uncertainty

Appropriate Use of Antimotility Agents

Many practitioners have had a philosophy that diarrhea is a protective body response and is functional in aiding the body to rid itself of toxins, and common treatments in the 1800s consisted of emetico-cathartics.[37] A variation of this thought process has support today with respect to the use of antimotility agents. Many believe reducing gut motility will increase the duration of illness by prolonging exposure to the offending agent.[45] One early study on the use of the antimotility agent Lomotil found an adverse effect when it was used as therapy for shigellosis.[46] The authors concluded that when the causative organism was a bacterial pathogen that must penetrate the intestinal epithelium to produce illness, intestinal motility may decrease the contact time between the invasive bacteria and mucosal cells, therefore Lomotil, which slows gut transit time, may be contraindicated in shigellosis. Some current recommendations still follow this philosophy that gut motility should not be slowed when infection is due to an invasive organism and do not advocate antimotility use with dysentery.[9,23] However, an inpatient double-blind, placebo-controlled, randomized clinical trial demonstrated ciprofloxacin and loperamide were effective and safe in the treatment of bacillary dysentery.[47] Other studies have shown similar results of the safe use of loperamide along with an antibiotic resulting in a faster resolution of diarrhea although most restrict enrollment to nondysenteric illness,[41] and a recent review article also recommended the use of loperamide as a conservative approach for dysentery only if combined with an antibiotic and the traveler had no toilet access.[48] Because of the conflicting opinions and data in this area, more research may be required to investigate both efficacy and safety of the antimotility plus antibiotic combination therapy with dysentery.

Expedient and Judicious Use of Treatment in Deployment Settings

In the civilian sector, the standard of care is to provide pretravel counseling advice on TD risk avoidance measures and a prescription of antibiotics and/or an antimotility agent for empiric stand-by therapy. For deployed military personnel, however, there are points for discussion. It is probably not practicable or desirable to provide every deploying troop with antibiotics to

self-treat in case he or she should develop TD. The misuse of provided antibiotics, potential negative consequences of masking a population deployment health event (outbreak), and antibiotic resistance are a few likely pitfalls of providing antibiotics for self-treatment. Furthermore, the military is unique in that troops travel with a designated medical provider deployed to support the health maintenance of the unit. Studies to date, however, have found there is much room for improvement in this area of management and practice policy given that most troops do not seek care for their diarrhea (despite the resulting performance impact and time lost),[4,5,49] and that when they do seek care, they are often provided a variable range of treatment regimens frequently inconsistent with published guidelines.[4,50] This is an area where further translational research should be conducted to incorporate previously gained knowledge from studying the problem of TD in deployed settings into best management strategies. Novel solutions must be considered, including development of Department of Defense (DoD)-wide standard practice guidelines with provision of antibiotics and treatment algorithms at the level of the corpsman and medic, coupled with the education of troops addressing when and why they should seek care.

Existing Guidelines

Many studies performed over the years have shown the efficacy of various treatment regimens for TD leading to a general consensus among experts for recommended treatment. Treatment summaries and guidelines have been published by various organizations.[9,23,51,52]

The Infectious Diseases Society of America (IDSA) addresses the subject of TD and considering the usual self-limited aspect of TD their current recommendation is a cautious approach, ensuring maintenance of hydration as a cornerstone of therapy. They recommend travelers requiring rapid control of symptoms because of circumstances (such as lengthy periods without access to toilet facilities) be instructed to use symptomatic treatment with an antimotility or antisecretory agent. Specific antimicrobial therapy is recommended when the diarrhea is moderate to severe or suggestive of an invasive pathogen. The combination of an antimicrobial treatment and the antimotility agent loperamide is recommended as an option only for older children and adults when there is no fever or blood in the stool. If symptoms worsen or do not improve within a 48-hour period, travelers are instructed to seek medical consultation.

The Health Information for International Travel (Yellow Book) recommendations, published by the Centers for Disease Control and Prevention (CDC), are similar to those from IDSA, and also refer to studies that illustrate a combination of loperamide and an antibiotic is superior therapy to either agent alone.

Within the DoD, the U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) has distributed Technical Guide (TG) 273, titled *Diagnosis and Treatment of Diseases of Tactical Importance to U.S. Central Command*, which addresses the approach to the patient with diarrhea, though its dissemination and use among providers within and between services is uncertain.[53] An algorithm is provided, which starts treatment at the abrupt onset of uncomfortable diarrhea, defined as loose stools, abdominal cramps, and urgency. The algorithm categorizes the disease as mild, moderate, and severe, with treatment based on the category of diarrhea and symptoms present. Treatment options include loperamide alone for mild diarrhea with minimal symptoms, to a combination of fluoroquinolone antibiotics ± loperamide for moderate-to-severe diarrhea. Furthermore, it is stated in the TG that antibiotic therapy is most effective when given as soon as possible after onset of symptoms and self-treatment is recommended for mission essential personnel.

Conclusion and Recommendations

TD has been extensively studied and although the large amount of current evidence provides a general consensus among experts on a proper approach to the problem, there are still various opinions concerning the absolute best management of diarrheal illness. For deployed military units and similar populations there are unique considerations necessitating a different approach to TD than the management used for short-term civilian travelers, and therefore our recommendations differ slightly from civilian guidelines.

Education of providers and individual troops is a major element of the clinical treatment of TD for military units. Medical personnel should ensure everyone under their care understands the importance of presenting for care early in the course of a diarrheal illness. An emphasis on the importance of early treatment should improve compliance with early presentation, allowing prompt initiation of treatment which can limit the duration of illness.

Oral rehydration as a keystone of treatment for TD is of utmost importance in austere deployment situations. The use of an appropriate solution for oral rehydration to ensure proper electrolyte balance, optimize intestinal fluid absorption, and minimize the chance of prolonging illness with a component of osmotic diarrhea, is recommended. See Table II for a summary of ORS recommendations.

Symptomatic treatment alone, with loperamide or BSS, should not be used without antibiotic use unless the provider is reasonably sure the cause is viral rather than bacterial, or the

TABLE II. Summary of Recommendations for Treatment of TD Among Deployed Military Personnel

Educate troops on the benefits of seeking care early.
Early and judicious use of adequate oral rehydration solutions with low osmolarity and the capability of ensuring proper electrolyte balance.
Use single-dose antibiotics along with loperamide as treatment for cases of ambulatory watery diarrhea among deployed U.S. service members.
- If no resolution with single dose therapy, continue treatment for 3 days.
- Persistent or chronic diarrhea requires a work up for other causes of diarrhea.

TABLE III. Author's Recommendations for Antimicrobial Treatment of Acute Watery Ambulatory Travelers' Diarrhea for Deployed U.S. Military Personnel

	Preferred Regimens[a]	Treatment Duration	Labeled Indication[b]	Labeled dose[b]
Levofloxacin	500 mg by mouth	Single dose[c]	No	N/A
Ciprofloxacin	750 mg by mouth	Single dose[c]	Yes	No
Ofloxacin	400 mg by mouth	Single dose[c]	No	N/A
Azithromycin[d]	1,000 mg by mouth daily	Single dose[c]	No	N/A
	Alternative Antibiotic Regimens			
Rifaximin[e]	200 mg by mouth three times daily	3 days	Yes[e]	Yes
Ciprofloxacin	500 mg by mouth twice daily	5–7 days	Yes	Yes
Azithromycin[d]	500 mg by mouth daily	3 days	No	N/A
Cefixime	400 mg by mouth daily	3–5 days	No	N/A
TMP/SMX[f]	One double-strength tablet by mouth every 12 hours	5 days	Yes	Yes

For diarrhea persisting longer than 2 weeks, consider evaluation for parasites and or empirical antiparasitic therapy.
[a]All antibiotic regimens are in conjunction with loperamide, 4 mg first dose, and then a 2-mg dose after each loose stool, not to exceed 16 mg in a 24-hour period. [b]As per electronic Physician's Desk Reference accessed on www.PDR.net Website. [c]If symptoms are not resolved after 24 hours, complete a 3-day course of antibiotics. [d]Use empirically as first line in Southeast Asia and India to cover fluoroquinolone resistant *Campylobacter* or in other geographical areas if *Campylobacter* or resistant ETEC are suspected. [e]Indication for noninvasive *E.coli* only. (Do not use if clinical suspicion for *Campylobacter, Salmonella, Shigella*, or other causes of invasive diarrhea.) [f]Considered an alternative drug for patients allergic to the other antibiotics listed in this table (however, providers must be aware of potential antibiotic resistance for common bacterial pathogens).

clinical severity is mild. Additionally, since the vast majority of TD is due to bacteria, we highly recommend the early use of antibiotics along with effective oral rehydration. We also recommend adjunctive therapy with loperamide since such strong evidence supports the use of this combination therapy regimen.

The choice of which antibiotic to use empirically should be based on the most likely bacterial etiology with respect to geography. Single-dose antibiotic treatment has been shown to be effective and is our recommendation to help ensure compliance and minimize adverse effects. If the patient does not improve, a 3-day course can then be prescribed. More invasive organisms such as *Campylobacter* may require longer periods of treatment, although, in general, also respond well to single-dose therapy. See Table III for our treatment recommendations. For symptoms lasting beyond 14 days, further work-up for different infectious and noninfectious etiologies should be initiated.

This review article provides evidence-based recommendations on the preferred methods to treat acute ambulatory watery diarrhea for a deployed military population. Public health strategies to prevent diarrheal illness, the prophylactic use of antibiotics for selective populations, management of dysentery, persistent and chronic diarrhea, and other diarrhea issues will be addressed in future articles. If the above recommendations are adhered to, afflicted personnel will have a more rapid resolution of symptoms, a shorter duration of degraded performance, and lower requirement for sick-in-quarters or medical evacuation leading to improved overall mission capability and readiness of deployed military units.

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